REMARKS

Claims 1, 2, and, 39-41 are pending. In the final Office mailed July 9, 2009, claim 2 is objected to. Claims 1 and 39-41 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Van den Heuvel et al., Am J Hum Genet. 62:262-268, 1998 ("Van den Heuvel") in view of U.S. Patent No. 6,040,138 ("the '138 patent"). Claims 1, 2, and 39-41 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Application Publication No. 2006/0099578 ("the '578 publication"), as evidenced by U.S. Patent No. 5,494,794 ("the '794 patent"), in view of Van den Heuvel and Smeitink, Bioessasy 23:518-525, 2001 ("Smeitink") and U.S. Patent Application Publication No. 2008/0187911 ("the '911 publication"). Each of these rejections is addressed below.

Claim objection

Claim 2 stands objected for reciting nonelected subject matter. Because claim 1 is under consideration and generic with respect to the nucleic acid molecules recited in claim 2, Applicants request that this objection be held in abeyance.

Rejections under 35 U.S.C. § 103(a)

Claims 1 and 39-41 are rejected as being obvious over Van den Heuvel in view of the '138 patent, and claims 1, 2, and 39-41 are rejected as being obvious over the '578 publication in view of Smeitink and the '911 publication. These rejections are traversed as follows.

In determining whether a claim is obvious, the Office must consider (a) the scope and content of the prior art, (b) the differences between the claimed invention and the prior art; and (c) the level of ordinary skill in the prior art, as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Here, Applicants have discovered that subjects having bipolar disorder (BPD) exhibit reduced expression of nuclear genes encoding polypeptides of complexes I-V of the mitochondrial respiratory chain.

Accordingly, the present invention is directed to an array where 90% of the nucleic acids are nuclear encoded genes of complexes I-V or are fragments thereof. The requirement that 90% of the nucleic acids are such nuclear encoded genes necessarily means that such arrays can include only a limited number of mitochondrial-encoded genes of complexes I-V and would necessarily result in the exclusion or omission of mitochondrial-encoded genes from the array.

The references cited by the Office, by contrast, are directed to analysis of mitochondrial function in general. An array useful for the study of mitochondrial function, rather than BPD, would not omit certain mitochondrial genes encoding subunits of complexes I-V. Rather, such an array would also include the mitochondrial-encoded genes of complexes I-V, as well as other nuclear genes encoding proteins involved in mitochondrial function. Because the cited references focus on mitochondrial function, they fail to teach or suggest the claimed array. Thus, no combination of these references can render the present claims as being obvious.

Van den Heuvel in view of the '138 patent

Claims 1 and 39-41 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Van den Heuvel in view of the '138 patent. In making this rejection, the Office cites Van den Heuvel as teaching a mutation in the human nuclear gene encoding the AQDQ subunit of complex I and concludes that Van den Heuvel teaches the use of only nuclear genes to detect a pathogenic mutation. Because Van den Heuvel does not teach placing nucleic acids on an array, the Office cites the '138 patent as providing this teaching.

Applicants respectfully traverse this rejection. Van den Heuvel does not teach the use of only nuclear genes but, rather, is focused on identification of mutations that result in complex I deficiency, be they nuclear or mitochondrial in origin. Van den Heuvel (page 262, right column, second full paragraph) notes that complex I includes more than 41 subunits, seven of which are encoded by the mitochondrial genome. A search for a

genetic defect in complex I would therefore include analysis of both nuclear encoded and mitochondrial encoded subunits. While Van den Heuvel describes the identification of a specific mutation in the AQDQ subunit of complex I, there is no suggestion to examine only this particular gene or to examine only nuclear encoded genes of complex I. Therefore Van den Heuvel provides no basis on which to design the claimed array.

The '138 patent does not overcome the deficiency of Van den Heuvel. The '138 patent is cited as teaching arrays. Nothing in this reference relates to genes involved in mitochondrial function. This combination of references therefore cannot render claim 1, or its dependent claims, as being obvious.

The '578 publication in view of Smeitink and the '911 publication

The Office also rejects claims 1, 2, and 39-41 as being unpatentable over the '578 publication, as evidenced by the '794 patent, in view of Smeitink and the '911 publication. In making this rejection, the Office cites the '578 publication as teaching a microarray consisting of probes for mitochondrial genes, including genes drawn to mitochondrial energy. Smeitink is cited as teaching that the percentage of patients with mitochondrial DNA abnormalities is relatively low and that screening for common mtDNA mutations in patients with an established oxidative phosphorylation disorder is unsatisfactory. The '911 publication is cited as teaching a microarray from which the mtDNA genes were removed. Applicants traverse this rejection as follows.

The primary reference, the '578 publication, teaches arrays for use in studying mitochondrial function. Arrays containing both nuclear and mitochondrial genes involved in mitochondrial biology are disclosed (see, page 11, Example 1 and Table 3). There is no disclosure of an array where at least 90% of the nucleic acid molecules are nuclear encoded genes that encode polypeptides of complexes I-V or fragments thereof. Nor is there any reason provided in the '578 publication for excluding some or all of the

mitochondrial genes from analysis of mitochondrial function. Indeed, if anything, the reference teaches the opposite.

The first secondary reference, Smeitink, also focuses on mitochondrial deficiencies, particularly on defects in oxidative phosphorylation (complexes I-V). Smeitink makes it clear that such defects can result from mutations in either nuclear or mitochondrial DNA; see, e.g., Figure 2 on page 523. This reference, like the '578 publication, also suggests that both nuclear *and* mitochondrial DNA should be analyzed when looking for genetic defects in mitochondrial function. These teachings would therefore not lead one to produce an array of the present invention. While the Office cites Smeitink as stating that the frequency of patients with mtDNA mutations is relatively low, Smeitink certainly does not stand for the proposition that mtDNA mutations should be ignored. The combination of the '578 patent and Smeitink therefore does not teach or suggest the claimed array.

The other secondary reference, the '911 publication, is cited as teaching an array on which mtDNA has been removed. Like the '578 publication and Smeitink, this reference also focuses on mitochondrial function. There is, however, no focus on the nuclear genes encoding polypeptides of complexes I-V. The '911 publication rather makes it clear that the disclosed arrays "encompass *all* the factors that will affect mitochondrial biogenesis and assembly (replication) and mitochondrial function under any physiological or pathophysiological conditions." The '911 publication, page 4, paragraph 45, emphasis added. If anything, the '911 publication suggests something quite different from the array of the present invention, i.e., that all factors involved in mitochondrial function should be included on an array.

In citing this publication, the Office points to Example 3, which notes that the 13 mtDNA genes were removed from filters (arrays) containing nuclear encoded genes. However, removal of these 13 genes neither results in nor suggests an array of the present invention. The arrays of the '911 publication contain many other genes in addition to

those encoding polypeptides of complexes I-V. Further, the '911 publication indicates that the mtDNA genes were analyzed on a separate array. Like the '578 publication and Smeitink, this publication fails to provide any reason for one to examine only the nuclear encoded genes of complexes I-V. Thus, this reference, either alone or in combination with the '578 publication and Smeitink, fails to teach an array of the present invention. This combination of references therefore cannot render the present claims as being obvious.

Summary

None of the references cited by the Office teaches or suggests measuring expression of only the nuclear encoded genes of complexes I-V. Absent this teaching, no combination of references cited by the Office can render the pending claims as being obvious. Withdrawal of both § 103(a) rejections is therefore respectfully requested.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 09 September 2009

Karen L. Elbing, Ph.D.
Reg. No. 35,238

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045